12. (amended) The mixture of claim [32] 33 wherein said chemical substituents [are electrophilic] comprise a leaving group prior to substitution on said heterocyclic scaffold.

13. (amended) The mixture of claim [32] 33 wherein at least one functionalizable atom of said heterocyclic scaffold is chemically blocked with a protecting group.

Please add claims 34-36 as follows:

--34. The mixture of claim 33 wherein said heterocyclic scaffold is fully or partially saturated by reaction with hydrogen.

35. The mixture of claim 33 wherein said compounds are further modified by substituting an existing chemical substituent L with another chemical substituent L.

36. The mixture of claim 33 wherein said chemical substituents of said compounds are further modified by atom abstraction.--

REMARKS

A request for a one month extension of time in which to respond to the Office Action is filed simultaneously herewith, including appropriate payment.

Upon entry of the amendments described above, claims 2-13, 24-26, and 33-36 remain pending. Claims 14-19 and 32 have been canceled. Claims 2-13 and 24-26 have been amended. Claims 33-36 have been added. No new matter has been added.

Support for claims 33-36 can be found throughout the specification. In particular, support for claim 34 can be found in the specification on page 7, lines 20-28 and on pages 42-43. Support for claim 35 can be found in the specification, for example, on page 7, lines 20-28 and in the chemical equations on at the bottom of page 54 and at the top of page 55. Support for claim 36 can be found in the specification, for example, on page 7, lines 20-28 and also in the chemical equations at the top of page 54.

The disclosure has been objected to with regard to chemical structures on pages 35 and 38 having atoms with unfilled valencies. The structures have been appropriately corrected by amendment.

Claims 14-16 have been objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully disagree because elements of the claims 14-16 are further limited with respect to the claims from which they depend. However, in order to advance prosecution, claims 14-16 have been canceled. Accordingly, the standing objection is rendered moot.

Claims 2-19, 24-26, and 32 have been rejected under 35 USC §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Office Action states that the amended claims introduce new matter. Applicants respectfully disagree because the amended claims are well supported by the specification.

With respect to claim 32 as a whole, the Office Action states that the claim encompasses mixtures having more than one of structures I, II, or III present, which contrasts with the original claim language. Applicants respectfully disagree and believe that the claim language is consistent with the specification and original claims. However, claim 32 has been canceled and replaced with claim 33, having alternate phraseology, so as to advance prosecution of the present application.

With respect to the tether "T," the Office Action states that the formula for T does not appear to be supported in the specification. Applicant respectfully points out that the tether is taught in the specification, for example, on page 3, line 26 to page 4, line 3, and also on page 5, line 25 to page 6, line 2. The specification also discloses that the tether may be, among other forms, straight chain, branched, cyclic, or heterocyclic, as defined on page 16, lines 17-34. However, claim 32 has been canceled and replaced with claim 33 having an amended description of T in order to advance prosecution of the present application. Support for the amendment is provided, in addition to the passages mentioned above, for example, on page 15, lines 5-13, and in the text and figures on pages 27, 34, 39, 41, 44-47, 49, and 50-52

The Office Action further states that there is no support in the original disclosure for mixtures of structures I, II, or III described in claim 32 because there appears to be no support for the use of the specific sites on the pyrimidine and purine nuclei in combination with the tether moieties and the specific L moieties claimed. Although claim 32 has been canceled, Applicant respectfully points out that the chemical structures of claim 32 are amply described in the specification. For instance, compounds of structure I are disclosed in Example 95-117, page 113, line 8 to page 123, line 8. In addition, compounds of structures II and III are described in Examples 4-94, on page 58 to page 113, line 7. More specifically, compounds of structure II wherein e is zero are described in Examples 89-97, and compounds of structure II wherein j is zero are described in Examples 11-55.

The Office Action further states that claims 17 and 18, which describe further substitution of the compounds of the mixture, are not supported in the disclosure. As these claims have been canceled, this rejection is now moot.

Claims 2-19, 24-26, and 32 have been rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that claim 32 contains the vague and indefinite terms of "conjugate group," "drug," "metal coordination group," "nucleosidic base," and "amino acid side chain." Despite the cancelation of claim 32, Applicants respectfully point out that conjugate groups and metal coordination groups, which are well known to those skilled in the art, are specifically exemplified in the specification on, for example, page 17, line 27 to page 18, line 3 and on page 18, lines 17-24. Accordingly, these terms are not vague and indefinite. Further, nucleosidic bases and amino acid side chains are well known to those skilled in the art as a finite number of molecules (*e.g.*, there are 20 naturally occurring amino acids and thus 20 amino acid side chains), all of which can be readily envisioned or determined by one skilled in the art. In addition, "drug" is well known by those skilled in the art as encompassing those molecules with pharmaceutical activity. Therefore, these terms are not vague and indefinite and the metes and bounds of the claimed mixtures are well determined.

The Office Action states that claim 32 is vague and indefinite because it is unclear what comprises the claimed mixtures. Although Applicant does not necessarily concur with this view, claim 32 has been canceled thereby rendering this rejection moot.

The Office Action further states that claims 7 and 9 are vague and indefinite because it is unclear what structures are encompassed with regard to the term "nucleophilic." Applicants respectfully disagree and point out that the art-skilled would readily recognize a nucleophilic species as previously set forth in Applicants' remarks on October 6, 1999. Therefore, the metes and bounds of the mixtures claimed are well defined. Both claims 7 and 9, however, have been amended in order to advance prosecution of the application. Support for the amendment can be found in the specification on, for example, page 7, lines 35-37.

The Office Action states that claim 10 is vague and indefinite with regard to the substituted tether moieties of the compounds. Applicants respectfully assert that the substituted tether moieties are readily discernable by one skilled in the art and that the claim is clear and definite as written. Since claim 10 has been amended, the present rejection is moot. Amended claim 10 finds support throughout the disclosure, for example, on pages 12, line 17 to page 13, line 19.

The Office Action states that claim 13 is vague and indefinite. Applicants respectfully disagree because the claim as written is clear with respect to its intended meaning. However, in order to advance prosecution, claim 13 has been amended. Support for the amendment can be found in the specification, for example, on page 18, line 25 to page 19, line 23.

The Office Action further states that claims 11 and 12 are vague and indefinite because the claims recite mixtures wherein at least one of the functional atoms on the heterocyclic scaffold is electrophilic. Applicants respectfully point out that this statement is erroneous as claims 11 and 12 actually recite *chemical substituents* that are electrophilic, not functional atoms. Nevertheless, claims 11 and 12 have been amended in order to advance prosecution, and support for the amendment can be found in the specification on, for example, page 6, lines 21-26 and page 13, line 26 to page 14, line 30.

The Office Action states that claims 17 and 18 are vague and indefinite. As both claims have been canceled, these rejections are moot.

The Office Action states that claim 18 is vague and indefinite with respect to the term "heterocyclic portion." Claim 18 has been canceled and thus this rejection is moot.

The Office Action states that claim 19 is indefinite. Since this claim has been canceled, this rejection is moot.

The Office Action further states that claims 11, 12, 13 and 18 have insufficient antecedent basis for certain terms. Claims 11-13 have been amended to properly refer to elements of the claims from which they depend, and claim 18 has been canceled.

Claims 2-3, 5-15, 17-19, and 32 stand rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Pavia *et al.* (referred to hereinafter at "Pavia"). The Office Action asserts that the present mixtures read on the compounds disclosed in Pavia. Applicant respectfully disagrees because Pavia's scaffolds comprise *two unsaturated* ring structures that are clearly distinct from the scaffolds of the present invention which may comprise *one unsaturated* ring (i.e., pyrimidine) optionally substituted with a saturated heterocycle. In addition, purine scaffolds are not disclosed in Pavia. As Pavia does not disclose the mixture of compounds of the present invention, Applicant submits that this rejection is improper. Accordingly, it is respectfully requested that this rejection be withdrawn.

In addition, claims 2-3, 5-15, 17-19, and 32 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pavia in view of Gordon *et al.* (hereinafter referred to as "Gordon"). The Office Action states that even if the pyrimidine compounds of the present invention are not explicitly disclosed in Pavia, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to form the combinatorial mixtures because Gordon teaches that split and combine synthesis techniques were well established in the art at the time of the invention. Applicant believes the rejection is improper as it is well established that to support *prima facie* obviousness under 35 U.S.C. 103, each and every element in the claims must be taught or suggested in the prior art and that there must be some motivation to modify or combine the prior art found in the references or in the knowledge of one skilled in the art. Specifically, Pavia does not disclose the compounds of the present invention for the reasons stated above (*i.e.*, scaffolds having two unsaturated rings in contrast to the pyrimidine compounds of the present invention which

comprise one unsaturated ring), and Gordon does not disclose a pyrimidine scaffold. Thus, as neither Pavia nor Gordon, used individually or in combination, disclose all limitations of the pyrimidine scaffolds of the present invention, these references do not render the rejected claims unpatentable. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the current rejection.

Claims 2-5, 7-15, 19, 26, and 32 stand rejected under 25 U.S.C. § 103(a) as being unpatentable over Freeman *et al.* (hereinafter "Freeman"), Kraatz *et al.* (hereinafter "Kraatz"), Drabex, and Moore in view of Henrie *et al* (either US 5,587,379 or 5,521192, hereinafter "Henrie") in further view of *In re Kerkhoven*, 626 F.2d 846, 850, 205. The Office Action asserts that Freeman, Kraatz, Drabex, and Moore disclose insecticidal pyrimidine compounds that read on structure I of the present invention. Further, the Office Action states that Henrie teaches mixtures of pyrimidine compounds for use as insecticidal mixtures. Applicant respectfully points out that a rejection based on obviousness cannot be maintained by merely suggesting, as does the Office Action, that one of ordinary skill in the art would have been motivated to combine the teachings of certain references.

It is established law that claims cannot be found obvious in view of prior art references unless the references themselves suggest that their respective teachings should be modified in a way that would produce the claimed invention. *Berghauser v. Dann*, 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). There must be something in the prior art that would have motivated persons of ordinary skill to make any necessary modifications. *In re Stencel*, 4 U.S.P.Q.2d 1071, 1073 (Fed. Cir. 1987), *accord*, *Ex parte Marinaccio*, 10 U.S.P.Q.2d 1719 (Pat. Off. Bd. App. 1989). In this respect, the following statement by the Patent Office Board of Appeals is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing

> evidence of the motivating force that would ***impel*** one skilled in the art to do what the patent applicant has done. *In re Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993) (citations omitted; emphasis added).

Applicant respectfully points out that in order to establish a *prima facie* case of obviousness, all of the elements of the rejected claims must be taught or suggested in the prior art. The mixtures of the present invention require *six or more* compounds. None of the cited references disclose the pyrimidine mixtures comprising six or more pyrimidine compounds, nor is there any suggestion to prepare mixtures of six or more pyrimidine compounds. As the mixtures of compounds of the present invention are not disclosed in the cited references, rejection under 35 U.S.C. § 103 is improper. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 32, 2-10, 13-15, and 17 stand rejected under 25 U.S.C. § 103(a) as being unpatentable over Summerton *et al.* (hereinafter "Summerton"). The Office Action states that Summerton teaches libraries having morpholine substituted purine heterocycles which read on the purine heterocyclic scaffold of the instant invention. The Office Action further asserts that it would have been obvious to one of ordinary skill in the art to prepare a mixture comprising at least six of these morpholino compounds having adenine as a nucleobase. Applicants respectfully point out and emphasize that Summerton does not teach all the elements of the presently rejected claims. Accordingly, this rejection under 35 U.S.C. § 103 is improper. Specifically, Summerton teaches morpholino oligomers having nucleobase substituents. In some aspects, the nucleobase may be adenine, and the Office Action asserts that such oligomers read on the purine compounds of the present invention wherein the adenine portion is the purine scaffold and the substituted morpholino oligomer portion is comparable to a chemical substituent or a tether bearing a chemical substituent. However, purine compounds of the present invention are all substituted at position 2 on the heterocycle and in some cases position 8 with -T-L. Adenine does not comprise substituents at these positions. Since Summerton does not disclose substitution at the 2- and 8- positions on adenine, every element of the claimed mixtures is not disclosed. Furthermore, Summerton does not provide legally sufficient motivation to modify adenine by substitution. In fact, substitution of adenine would likely result in less desirable oligomers since they are designed to form Watson-Crick base pairs with target nucleic

acids (see Summerton, col. 4, lines 22-25). In view of these remarks provided above, Applicant respectfully requests that this rejection be withdrawn.

Claims 32, 2-10, 13, 17 and 24-26 stand rejected under 25 U.S.C. § 103(a) for allegedly being unpatentable over Neilsen *et al.* (hereinafter "Neilsen"). The Office Action states that Neilsen teaches libraries of PNAs comprising purine heterocycles (as "scaffolds") such as nucleobases A and G wherein the remaining PNA portion can be considered an L group capable of hydrogen bonding. The Office Action further asserts that it would have been obvious to one of ordinary skill in the art to prepare a mixture comprising at least six PNAs having A or G as a nucleobase. Applicants disagree because Neilsen does not teach the elements of the presently rejected claims and, therefore, the rejection under 35 U.S.C. § 103(a) is improper. For instance, the purine compounds of the present invention are all substituted at position 2 on the purine heterocycle and in some cases position 8 with group -T-L. Adenine does not comprise substituents at these positions and guanine does not comprise a substituent on the 8-position of the purine ring. As Neilsen does not teach substitution at the 2- and 8- positions on adenine or the 8-position on guanine, every element of the claimed mixtures is not disclosed. In addition, Neilsen does not provide legally sufficient motivation to modify adenine or guanine by substitution. In fact, substitution of the bases would likely result in less desirable oligomers as they are designed to hybridize with target nucleic acids (see Neilsen, col. 2, lines 50-52). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Applicant notes that the initialed form PTO-1449 indicates the Examiner's position that references BN, BO, BT, CJ and DR were not provided. To the contrary, these references were submitted to the Patent Office on July 31, 1998. Moreover, these references were received by the Patent Office on August 3, 1998, as evidenced by the stamped receipt postcard, a copy of which is herewith provided. However, for the Examiner's convenience, Applicant hereby provides additional copies of references BN, BO, BT, CJ and DR cited on form PTO-1449.

It is believed that all of the claims presently before the Examiner patentably define the present invention over the prior art and are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,

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